Effects of Serotonin on Blood Glucose and Insulin Levels of Glucose- and Streptozotocin-Treated Mice

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Abstract—Effects of serotonin (5-HT) on plasma glucose and serum insulin levels were studied in mice. In normal mice, 5-HT induced a dose-dependent hypoglycemia and an increase in serum insulin levels. 5-HT significantly inhibited glucose-induced hyperglycemia and increased glucose-stimulated insulin release. However, in streptozotocin-induced diabetic mice, 5-HT changed neither the glucose nor insulin levels. These results strongly suggest that 5-HT-induced hypoglycemia is brought on by increasing serum insulin levels.

It has been suggested that some neurotransmitters, such as noradrenaline or acetylcholine, regulate the blood glucose through mechanisms involving the release of pancreatic hormones (1, 2). Serotonin (5-HT) is also known to be a neurotransmitter that plays an important role in several physiological functions. In previous studies (3, 4), 5-HT has been shown to have differential effects on blood glucose levels, that is, hyperglycemic or hypoglycemic effects. In mice, it has been demonstrated that 5-hydroxytryptophan (5-HTP), the precursor of 5-HT, produces hypoglycemia, and the effects of 5-HTP are due to the formation of 5-HT (5, 6). In addition, it is reported that the hypoglycemic effects of 5-HTP are accompanied with an increase of insulin levels (5, 6). Recently we found that 5-HT induces hypoglycemia and hyperinsulinemia in fasted mice, and its effects involve 5-HT receptors (7). These findings lead to the possibility that 5-HT may involve the regulation of blood glucose by facilitating insulin release. However, previous studies have demonstrated that endotoxin-induced hypoglycemia may be due to the accumulation of 5-HT in the liver (8) and that 5-HT can inhibit gluconeogenesis in isolated hepatic cells (9). Thus, possible mechanisms in the liver may also contribute to the hypoglycemic effects of 5-HT. In this paper, therefore, to clarify the involvement of insulin in hypoglycemia induced by 5-HT, we investigated the effects of 5-HT on blood glucose and insulin levels using glucose- and streptozotocin-treated mice.

Male ddY mice weighing 25–30 g were purchased from SLC Japan, Inc. (Shizuoka, Japan). Mice were housed in a room with a controlled 12 hr/12 hr light/dark cycle, with lights on between 7:00 a.m. and 7:00 p.m., a temperature of 24±1 °C and at a humidity of 55±5%. Experiments were performed between 1:00 and 5:00 p.m. Mice were starved for 18–20 hr before the injection of 5-HT. Serotonin creatinine sulfate monohydrate (5-HT) and glucose were purchased from Merck (Darmstadt, West Germany) and Wako Pure Chemical Industries (Osaka, Japan), respectively. 5-HT and glucose were dissolved in saline and given i.p. simultaneously. Streptozotocin was obtained from Sigma Chemical Co. (St. Louis, U.S.A.). Streptozotocin was freshly dissolved in ice-cold citrate buffer (pH 4.5) and administered i.v. from the tail vein. Streptozotocin at 250 mg/kg was injected 7 days before the injection of 5-HT. Drugs were given at a volume of 0.1 ml/10 g body weight. Blood samples were taken from the caudal vena cava under light ether anesthesia.
30 min after the injection of 5-HT. Only one sample was removed from each mouse. Plasma glucose was determined with glucose oxidase and peroxidase using a Wako Glucose C-test kit from Wako Pure Chemical Industries (Osaka, Japan). Serum insulin levels were determined as immunoreactive insulin (IRI) using a double-antibody radioimmunoassay kit (Insulin RIA Beads, Dinabot RI Institute, Tokyo, Japan). Statistical significance was evaluated by Student's t-test between two groups. For three or more groups, analysis of variance was performed followed by Duncan's multiple range test or Dunnet's test when appropriate.

Figure 1 shows the effects of 5-HT on the plasma glucose and serum insulin levels of normal mice. 5-HT produced a significant hypoglycemia and increase in serum insulin levels. Both effects were elicited above the dosage of 20 mg/kg. The administration of 5-HT at 120 mg/kg induced about a 49% decrease in plasma glucose and about a 184% increase in serum insulin levels compared to the control group.

Figure 2 demonstrates the effects of 5-HT on plasma glucose and serum insulin levels in glucose and streptozotocin-treated mice. Glucose at 1 g/kg induced significant increases in glucose and insulin levels. 5-HT significantly reduced glucose-induced hyperglycemia and enhanced insulin release stimulated by glucose. Streptozotocin at 250 mg/kg induced a remarkable hyperglycemia and a significant decrease in insulin levels. However, 5-HT affected neither the plasma glucose nor the serum insulin levels of streptozotocin-induced diabetic mice.

We previously reported that 5-HT induces dose-dependent hypoglycemia in fasted mice (7). As shown in Fig. 1A, we confirmed the effects of 5-HT on plasma glucose. In this study, we found that the hyperinsulinemic effects of 5-HT are also dose-dependent (Fig. 1B). It has been reported that 5-HTP, the precursor of 5-HT, causes hypoglycemia and hyperinsulinemia in mice, and its effects are due to the formation of 5-HT (5, 6). The effects of 5-HT in our present results support these previous findings. As shown in Fig. 1, it seems that hyperinsulinemia is concomitant with hypoglycemia. This indicates that hyperglycemia elicited by 5-HT may be brought on by increasing insulin release.

To elucidate the involvement of insulin in 5-HT-induced hypoglycemia, we examined the effects of 5-HT in glucose- and streptozotocin-treated mice. Previous studies indicated that 5-HT enhances or decreases glucose-induced insulin release among different species or experimental conditions (3, 10, 11), although the reason for these discrepancies remains unclear. As shown in our results, 5-HT inhibited glucose-induced hyperglycemia and enhanced the increase in serum insulin levels elicited by glucose. It indicates the involvement of insulin in the hypoglycemic effects of 5-HT in mice. Streptozotocin is recognized to induce diabetes in experimental animals characterized.

![Fig. 1. Dose response effects of 5-HT on plasma glucose and serum insulin levels of mice. (A): Plasma glucose, (B): Serum IRI. Results are shown as the mean±S.E. (N=7–10). 5-HT was given i.p. Blood samples were taken 30 min after the injection of 5-HT. *P<0.05, **P<0.01, significant difference from the control.]
by hyperglycemia and hypoinsulinemia, since it destroys pancreatic B cells and decreases the stores of insulin (12). As shown in Fig. 2, streptozotocin induced remarkable hyperglycemia and significant decreases in serum insulin levels. However, 5-HT did not induce hypoglycemia nor hyperinsulinemia in streptozotocin-treated diabetic mice. It strongly suggests that the effects of 5-HT are dependent on insulin release. Taken together, it leads to the conclusion that hypoglycemia induced by 5-HT is elicited by increasing insulin release.

5-HT is known to be abundantly present in the pancreatic islets of several species including mice, rats or rabbits (13). In addition, it has been demonstrated that pancreatic islets have mechanisms for the uptake of 5-HT and form 5-HT from the precursor 5-HTP (14, 15). These evidence together with our present results suggest that 5-HT may control the blood glucose levels by affecting the mechanisms for insulin release in pancreatic B cells. It is probably mediated by 5-HT receptors, since we have demonstrated in our previous study (7) that 5-HT receptors may be involved in the hypoglycemic and hyperinsulinemic effects of 5-HT. Our results

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**Fig. 2.** Effects of 5-HT on plasma glucose and serum insulin levels in glucose- and streptozotocin-treated mice. (A): Plasma glucose, (B): Serum insulin. Results are shown as the mean±S.E. (N=6-12). 5-HT was given i.p. at 80 mg/kg. Glucose at 1 g/kg was given i.p. Glucose and 5-HT were injected simultaneously. Streptozotocin at 250 mg/kg was given i.v. at 7 days before the injection of 5-HT. Blood samples were taken 30 min after the injection of 5-HT. **P<0.01, ***P<0.001, significant difference from the saline administered mice of the respective group. *P<0.05, **P<0.01, significant difference from the saline administered normal mice.
implicate the presence of 5-HT receptors in pancreatic B cells and further detailed studies are required. In addition, we have shown that 5-HT affects the effects of glucose. Therefore, there is increasing interest in the possibility that 5-HT may interact with drugs or endogenous substances which modify blood glucose levels.

References